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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/518,503
Filing Date: December 20, 2004
Appellants: EGGENWEILER ET AL.

HARRY B. SHUBIN
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal Brief filed Aug. 11, 2008 appealing from the Final Office action mailed Jan. 11, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the Brief is correct.

(4) Status of Amendments After Final

Appellants' statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

Appellants' statement of the grounds of rejection for review on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Foreign Patents

- EP 731,099

Non-Patent Literature

- Wikipedia, COPD, downloaded 06-26-2007, <http://en.wikipedia.org/wiki/COPD>.
- Wikipedia, IBD, downloaded 06-26-2007, <http://en.wikipedia.org/wiki/IBD>.
- Wikipedia, Rolipram, downloaded 8/20/2008, http://en.wikipedia.org/wiki/Rolipram. (Full citation attached.)
- Dyke, et al., Exp. Opin. Invest. Drugs 8:1301-1325 (1999).
- Hanifin, et al., Journal of Investigative Dermatology, 107(1):51-56 (1996).
- Griffiths, et al., British Journal of Dermatology 2002; 147:299-307.
- MacKenzie, Allergology International (2004) 53: 101-110.
- MedLinePlus <http://www.nlm.nih.gov/medlineplus/infections.html>, downloaded 06-29-2007.
- MedLinePlus <http://www.nlm.nih.gov/medlineplus/cancers.html>, downloaded 06-29-2007.
- Bernes, J. Allergy Clin. Immunol, Jul. 2000, pgs. 5-16.
- Kobayashi, et al., Mediators of Inflamm., Vol. 2007, Article ID 58901, 9 pgs.
- Reffelmann, et al., Circulation 2003:108;239-244.
- Rybalkin, et al., Circ. Res. 2002;90;151-157.

- Lehnart, et al., Cell, Vol. 123, 25-35, Oct. 7, 2005.
- Xu, et al., Invest. Ophthal. & Vis. Sci., April 1999, Vol. 40, #5, 842-950.
- Yamaki, et al., J. Pharm. & Parm., 2004, 56, 877-882. (Full citation attached.)
- Abbas, et al., Autoimmunity 2000, 32, 2, 93-99. (Full citation attached.)

(9) Grounds of Rejection

The following grounds of rejection are applicable to the appealed claims:

Rejection Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21, 24-26 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for treatment of allergic diseases, asthma, chronic bronchitis, atopic dermatitis, psoriasis or other skin diseases, inflammatory diseases, autoimmune diseases, sepsis, memory disorders, atherosclerosis, AIDS or myocardial disease (claims 21, 24, 25 and 30), coronary heart disease, reversible or irreversible myocardial ischaemia/reperfusion damage, acute or chronic heart failure or restenosis including in-stent restenosis and stent-in-stent restenosis (claim 26) and allergic diseases, asthma, chronic bronchitis, atopic dermatitis, psoriasis, rheumatoid arthritis, multiple sclerosis, Crohn's disease, diabetes mellitus, ulcerative colitis, osteoporosis, transplant rejection reactions, cachexia or

atherosclerosis (claim 30). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The present specification offers insufficient evidence that the claimed methods treat specific diseases/conditions susceptible to PDE-4 inhibition amelioration, although the claims encompass treatment of such diseases/conditions. The following reasons apply to this enablement rejection.

Pursuant to *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the prior art; (4) The level of one of ordinary skill; (5) The level of predictability in the art; (6) The amount of direction provided by the inventor; (7) The existence of working examples; and (8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue;" see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the methods.

The scope of the methods is the use of the trillions of thiazole compounds comprehended under formula I.

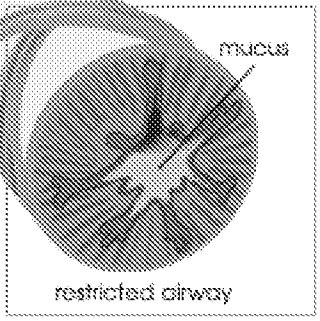
(b) Scope of the diseases covered.

The diseases covered by the rejected claims have been listed above. These diseases are discussed here to emphasize their scope and heterogeneity.

Allergic diseases encompass allergy-related conditions such as asthma, allergic rhinitis, eosinophil-associated diseases, food allergy, latex allergy, primary immune deficiency, sinusitis, stinging insect allergy, among others.

- **Allergic rhinitis (AR)** is a heterogeneous disorder that despite its high prevalence is often undiagnosed. It is characterized by one or more symptoms including sneezing, itching, nasal congestion, and rhinorrhea followed by congestion, fatigue, malaise, irritability, and possibly neurocognitive deficits. Many causative agents have been linked to AR including pollens, molds, dust mites, and animal dander. Seasonal allergic rhinitis (SAR) is fairly easy to identify because of the rapid and reproducible onset and offset of symptoms in association with pollen exposure. Perennial AR is often more difficult to detect than SAR because of the overlap with sinusitis, respiratory infections, and vasomotor rhinitis.
- **Eosinophil-associated diseases** and disorders encompass such diverse conditions as allergic diseases, atopic and related diseases, medication-related eosinophilias, parasitic infections (e.g., with helminthes), specific fungal infections, hematologic and neoplastic disorders, hypereosinophilic syndrome, leukemia, lymphomas, mastocytosis, skin and subcutaneous diseases, pulmonary diseases, gastrointestinal diseases, neurologic diseases, rheumatologic diseases, cardiac diseases, renal diseases, immunologic reactions, specific immune deficiency diseases, transplant rejection and hypoadrenalism.
- **Primary immunodeficiencies** are complex diseases including B cell deficiencies, combined T cell and B cell deficiencies, T cell deficiencies, defective phagocytes,

complement deficiencies, hyper-IgE syndrome and chronic mucocutaneous candidiasis. B cell deficiencies include disorders in which B cells make almost no antibodies, leaving the person susceptible to a wide range of infections, disorders in which B cells make not enough antibodies to give protection and disorders in which the B cells fail to make special subsets of anti-bodies, creating a risk for certain kinds of infections. In combined T cell and B cell deficiencies both antibodies and T cells are disabled, so nearly any infection is a threat to life. T cell deficiencies include *DiGeorge Anomaly* and *Cartilage Hair Hypoplasia. DiGeorge Anomaly* is a birth defect in which cells that give rise to various parts of the head and neck develop abnormally. Developmental changes can affect the face, parts of the brain, heart and thymus. *Cartilage Hair Hypoplasia* is an immune system abnormality linked to dwarfism. The child has abnormally short limbs and thin, sparse hair. The skin forms extra folds around neck, hands and feet, and joints are loose. Defective phagocytes include *Chronic Granulomatous Disease (CGD), Leukocyte Adhesion Defect (LAD), and Chediak-Higashi Syndrome (CHS). CGD* includes a group of inherited immunodeficiency diseases caused by faulty phagocytes, which are unable to produce oxygen-transporting compounds to kill certain types of germs. *LAD* causes recurrent, life-threatening infections because phagocytes are unable to migrate to an infection. These phagocytes lack a molecule that allows them to attach to blood vessel walls. Other white cells lack adhesion molecules, preventing them from attaching to target cells and surfaces. *CHS* is a rare and potentially severe disorder caused by defective phagocytes, platelets and melanocytes. Complement deficiencies often do



not cause disease until adulthood. Some complement deficiencies foster the same kinds of bacterial infections seen with antibody deficiencies, as well as immune system disorders such as SLE. Other complement deficiencies lead to an increase of blood-borne infections such as meningitis. **Cure is not possible, and there is no specific therapy for complement deficiencies.** *Hyper-IgE Syndrome* is a relatively rare condition characterized by extremely high levels of IgE in the blood. From infancy, children with Hyper-IgE are plagued by severe, recurrent abscesses, especially of the skin and lungs. *Chronic Mucocutaneous Candidiasis* is associated with other immunodeficiencies. Patients are unable to defend against *Candida* fungus and develop rashes and sores on skin, nails and mucous membranes.

Asthma is a disease of the lungs that affects bronchial tubes or airways; a reversible obstructive airway disease. Unlike other conditions that obstruct airways, such as cystic fibrosis, chronic bronchitis and emphysema, asthma does not affect sufferers all the time. During an asthma attack, membranes inside bronchial tubes release mucus and become inflamed, causing muscles to contract and create wheezing spasms. Attacks can be severe or relatively mild, but the condition is dangerous and can easily spiral out of control. Specific causes of asthma are far from straightforward. Asthma is divided into a number of different types:

- **Allergic Asthma:** Triggered by allergens, e.g., pet dander, pollen, dust mites, pollutants, wood dust, smoke, irritants, chemicals, viral infections, bacteria, stress, emotion, exercise.

- **Childhood Allergic Asthma:** Maternal smoking can contribute to asthma or other infant lung function impairment, even before a child is born. Continued exposure to cigarette smoking can irritate the respiratory tract, making infants and children particularly vulnerable to allergic asthma.
- **Intrinsic Asthma:** Allergies do not play a part; its typical onset occurs after age 40. Possible causes include respiratory irritants, e.g., perfumes, cleaning agents, fumes, smoke, cold air, upper respiratory infections, gastroesophageal reflux. Intrinsic asthma tends to be less responsive to treatment than allergic asthma.
- **Exercise-Induced Asthma:** Can affect anyone at any age and may be attributed to loss of heat and moisture in the lungs with strenuous exercise. Frequent coughing during exercise may be the only symptom, but exercise-induced asthma symptoms can be more severe in cold, dry conditions. Prophylactic medications can prevent onset of asthmatic symptoms for sensitive individuals.
- **Nocturnal Asthma:** Affects people during sleep, regardless of time of sleep. Symptoms can be triggered by allergens in bedding or bedroom, decrease in room temperature and gastroesophageal reflux.
- **Occupational Asthma:** Occurs as a result of breathing chemical fumes, wood dust, or other irritants over long periods of time.
- **Steroid-Resistant Asthma:** Overuse of asthma medications can lead to status asthmaticus, a severe asthma attack that fails to respond to medication and may require mechanical ventilation.

Chronic bronchitis is a chronic inflammatory condition in the lungs that causes respiratory passages to be swollen and irritated, increases mucus production and may damage the lungs. Symptoms are coughing and breathlessness, which worsens over years. It is defined as a chronic cough or mucus reproduction for at least three months in two successive years when other causes have been excluded.

Atopic dermatitis is a common chronic skin disease, with a hereditary component, often referred to as eczema, dermatitis or atopy. The atopic dermatitis triad includes asthma, allergies, hay fever and eczema. The skin becomes extremely itchy and inflamed, causing redness, swelling, cracking, weeping, crusting and scaling. Dry skin is very common and an underlying cause of some typical rash symptoms. It most often it affects infants and young children, although it may persist into adulthood or actually first show up later in life. Multiple factors can trigger or worsen atopic dermatitis, including dry skin, seasonal allergies, exposure to harsh soaps and detergents, skin products or creams and cold weather. Environmental factors can activate atopic dermatitis symptoms.

Psoriasis includes various forms, such as plaque, guttate, inverse, pustular and erythrodermic. Psoriasis may be defined by its location on the body, including scalp psoriasis, genital psoriasis, psoriasis on the face, on hands and feet and psoriasis of the nails; and psoriatic arthritis includes symmetric arthritis, asymmetric arthritis, distal interphalangeal predominant, spondylitis and arthritis mutilans.

Other skin diseases include such conditions as Acanthosis Nigricans, boils and carbuncles, Bullous Disease, common growths, corns and calluses, dandruff, Derm-

atographia, Dermatomyositis, dry skin, Granuloma Annulare, Graves' Dermopathy, Henoch-Schönlein Purpura, Ichthyosis Vulgaris, Intertrigo, Keratosis Pilaris, Lichen Nitidus, Lichen Planus, Mastocytosis, Molluscum (Molluscum Contagiosum), Neurodermatitis (Lichen Simplex Chronicus), Pityriasis Rosea, Epidermolysis Bullosa, Lichen Sclerosus, Seborrheic Dermatitis, Seborrheic Keratoses, Stevens-Johnson Syndrome, Sweet's Syndrome and unexplained Dermopathy (Morgellons),

Inflammatory diseases include Rheumatoid Arthritis (RA), Chronis Obstructive Pulmonary Disease, psoriasis, atherosclerosis and osteoarthritis. Ulcerative colitis and Crohn's disease are forms of an entire inflammatory disease family under the generic term, irritable bowel disease (IBD). IBD arises from a range of known and unknown causes. Ulcerative colitis and Crohn's disease are idiopathic.

Autoimmune disorder occurs when the immune system mistakenly attacks and destroys healthy body tissue. There are more than 80 autoimmune diseases including Hashimoto's thyroiditis, pernicious anemia, Addison's disease, Type I diabetes, RA, Systemic lupus erythematosus, Dermatomyositis, Sjogren syndrome, Lupus erythematosus, Multiple Sclerosis, Myasthenia gravis, reactive arthritis, Grave's disease, Celiac disease - sprue, polymyositis, scleroderma, vitiligo, glomerulonephritis and pulmonary fibrosis.

Sepsis is also known as blood poisoning, septicemia, blood stream infection. The presence of bacteria (bacteremia) or other infectious organisms or their toxins in the blood (septicemia) or in other tissue of the body. Sepsis may be associated with clinical symptoms of systemic illness, such as fever, chills, malaise, low blood

pressure, mental status changes, and can be life threatening. Treatment depends on the type of infection, but usually begins with antibiotics or similar medications.

Memory disorders comprise all impairment of understanding or skill disorders. These include acquired language disorders, such as aphasias (e.g., conduction aphasia), apraxia, dysarthria, alexia, receptive dysphasia, and agraphia. It includes many types of disorders called amnesias. There is anterograde amnesia (new events are not transferred to long-term memory) and retrograde amnesia (inability to recall events that occurred before the onset of amnesia). There is lacunar amnesia (loss of memory about one specific event), fugue amnesia (psychogenic amnesia or hysterical amnesia, including "repressed memories"), childhood amnesia (inability to remember events from early childhood), transient global amnesia (total memory loss), those arising from complex partial seizures and alcoholic blackouts. It also includes various agnosias, such as prosopagnosia, integrative agnosias, asogmatoagnosia, associative agnosias, time agnosia, apperceptive agnosia, object agnosia, finger agnosia, phonagnosia, central achromatopsia, topographical agnosia, dyslexia, dyscalculia, right-left disorientation, optic ataxia and ocular apraxia, color agnosia, simultanagnosia, anosognosia, auditory agnosia (including amusia and word meaning deafness), and somatosensory agnosia (including microsomatagnosia, macrosomatagnosia, tactile agnosias and astereoagnosia), constructional dyspraxia, and more general processing disorders such as cerebral visual impairment.

Atherosclerosis is a disease of the arterial wall in which the wall layer thickens, causing channel narrowing impairing blood flow. It can occur in any body area, but

is most crucial when it happens in the heart, brain or blood vessels to the brain. Narrowing is due to plaque formation in the inner artery lining. Plaques consist of low-density lipoproteins, decaying muscle cells, fibrous tissue, blood platelets clumps, cholesterol and sometimes calcium. They tend to form in turbulent blood flow regions and are found most often with high concentrations of cholesterol in the bloodstream. The number and thickness of plaques increases with age, causing smooth blood vessel lining loss and encouraging thrombi formation. Sometimes thrombi fragment to form emboli and travel through the bloodstream to block smaller vessels. Atherosclerotic interference with thrombi blood supply (stroke) is the third most common cause of death. Atherosclerosis also causes serious illness by reducing blood flow in other major arteries, such as to kidneys, legs and intestines.

AIDS is the abbreviation for acquired immune deficiency syndrome. The disease is caused by a virus known as the human immunodeficiency virus (HIV). Patients who acquire HIV will generally pass through the following states.

- During **Acute retroviral syndrome** the patient may have symptoms that can resemble mononucleosis, including fever, fatigue, muscle aches, loss of appetite, upset stomach, weight loss, skin rash, headache, and swollen lymph nodes. The symptoms develop between 1-6 weeks after infection and last for 2-3 weeks.
- HIV infection has a very long **latency period**, lasting for 10 years or more. During this period, the virus continues to reproduce in the lymph nodes and certain abnormal conditions and symptoms may develop, including Persistent Generalized Lymahadenopathy (PGL), constitutional symptoms (low-grade fevers, fatigue, general

weakness, and loss of appetite, as well as other symptoms) and problems with organs and tissues throughout the body (thrush, ulcers, open sores, diarrhea, malnutrition, destruction of lung, kidney and nervous system cells, general strength loss, loss of reflexes and feelings of numbness or burning sensations in feet or lower legs).

- During **Late-stage AIDS**, the virus has become very active and has started to cause massive damage to the immune system, with a sharp decrease in the number of CD4 lymphocytes. The patient also begins to have more frequent and more serious medical problems, such as infectious diseases, cancers and opportunistic infections. AIDS dementia complex usually occurs late in the progress of AIDS, marked by loss of reasoning ability, loss of memory, inability to concentrate, listlessness, and unsteadiness in walking. **There are no treatments for the condition.**

Myocardial diseases or cardiomyopathies are diseases of the myocardium associated with cardiac dysfunction. They are classified as dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, arrhythmogeníc right ventricular cardiomyopathy and others.

- Dilated Cardiomyopathy is characterized by dilatation and impaired contraction of the left or both ventricles. It may be idiopathic, familial/genetic, viral and/or immune, alcohol/toxic or associated with recognized cardiovascular disease where the degree of myocardial dysfunction is explained by the abnormal loading conditions or the extent of ischemic damage. Histology is nonspecific. Presentation is usually with heart failure which is often progressive. Arrhythmias, thromboembolism and sudden death are common and may occur at any stage.

- **Hypertrophic Cardiomyopathy** is characterized by left and/or right ventricular hyper-trophy, which is usually asymmetric and involves the interventricular septum. Typi-cally, left ventricular volume is normal or reduced. Systolic gradients are common. Familial disease with autosomal dominant inheritance predominates. Mutations in sarcomeric contractile protein genes cause disease. Typical morphological changes include: myocyte hypertrophy and disarray surrounding areas of increased loose connective tissue. Arrhythmias and premature sudden death are common.
- **Restrictive Cardiomyopathy** is characterized by restrictive filling and reduced diastolic volume of either or both ventricles with normal or near normal systolic function and wall thickness. Increased interstitial fibrosis may be present. It maybe idiopathic or associated with other disease (e.g. amyloidosis, endomyocardial disease with or without hypereosinophilia).
- **Arrhythmogenic Right Ventricular Cardiomyopathy** is characterized by progressive fibrofatty replacement of right ventricular myocytes, initially with typical regional and later global right and some left ventricular involvement with relative sparing of the septum. Familial disease is common with autosomal dominant inheritance and incomplete penetrance, a recessive form is described. Presentation with arrhythmias and sudden death is common, particularly in the young.
- **Unclassified Cardiomyopathies** include a few cases which do not fit readily with any group (e.g. fibroelastosis, noncompacted myocardium, systolic dysfunction with mini-mal dilatation, mitochondrial involvement). Some diseases may present with

features of more than one type of cardiomyopathy (i.e. amyloidosis, systemic hypertension). Arrhythmias and conduction disease may be primary myocardial disorders.

- **Specific Cardiomyopathies** describes heart muscle diseases associated with specific cardiac or systemic disorders.
- **Ischemic Cardiomyopathy** presents as a dilated cardiomyopathy with impaired contractile performance not explained by the extent of coronary artery disease or ischemic damage.
- **Valvular Cardiomyopathy** presents with ventricular dysfunction which is out of proportion to abnormal loading conditions.
- **Hypertensive Cardiomyopathy** often presents with left ventricular hypertrophy in association with features of dilated cardiomyopathy or restrictive cardiomyopathy with cardiac failure.
- **Inflammatory Cardiomyopathy** is defined as myocarditis in association with cardiac dysfunction. Myocarditis is an inflammatory disease of the myocardium, diagnosed by established histological, immunological and immunohistochemical criteria. Idiopathic autoimmune and infectious forms of inflammatory cardiomyopathy are recognized. Inflammatory myocardial disease is involved in pathogenesis of dilated cardiomyopathy and other cardiomyopathies e.g. Chagas', HIV, enterovirus, adenovirus and cytomegalovirus.
- **Metabolic Cardiomyopathy** includes the following categories: *Endocrine* (thyrotoxicosis, hypothyroidism, adrenal cortical insufficience, phaeochromyocytoms, acromegaly, diabetes mellitus); f*amilial storage disease and infiltrations* (haemochromato-

sis, glycogen storage disease, Hurler's syndrome, Refsum's syndrome, Niemann-Pick disease, Hand-Schuller-Christian disease, Fabry-Anderson disease, Morguio-Ullrich disease); d*eficiency* (disturbances of potassium metabolism, magnesium deficiency, and nutritional disorders such as Kwashiorkor, anemia, and beri-beri, selenium deficiency); and a*myloid* (primary, secondary, familial, and hereditary cardiac amyloidosis, familial Mediterranean fever, and senile amyloidosis).

- **Peripartal Cardiomyopathy** may first manifest in the peripartum period and is probably a heterogeneous group.

Coronary heart disease (CHD), also called coronary artery disease, is narrowing of small blood vessels that supply blood and oxygen to the heart. CHD is usually caused by atherosclerosis, when fatty material and plaque build up on artery walls. As coronary arteries narrow, blood flow to the heart can slow down or stop, causing stable angina, shortness of breath, heart attack and other symptoms.

Myocardial ischemia or ischemic heart disease (IHD), is characterized by reduced blood supply to the heart muscle, usually due to coronary artery disease (atherosclerosis of coronary arteries). Its risk increases with age, smoking, hypercholesterolaemia, diabetes, hypertension and is more common in men and those who have close relatives with ischemic heart disease. Symptoms of stable ischemic heart disease include angina and decreased exercise tolerance. Unstable IHD presents itself as chest pain or other symptoms at rest or rapidly worsening angina. Depending on symptoms and risk, treatment may be with medication, percutaneous coronary intervention (angioplasty) or coronary artery bypass surgery (CABG).

Heart failure means that the heart's pumping power is weaker than normal. Blood moves through the heart and body at a slower rate, and pressure in the heart increases. The heart cannot pump enough oxygen and nutrients to meet the body's needs. The heart chambers respond by stretching to hold more blood to pump through the body or by becoming more stiff and thickened. This helps to keep the blood moving for a short while, but in time, the heart muscle walls weaken and are unable to pump as strongly. As a result, kidneys often respond by causing the body to retain fluid and sodium. If fluid builds up in the arms, legs, ankles, feet, lungs or other organs, the body becomes congested, resulting in congestive heart failure.

Restenosis is recurrence of stenosis after corrective surgery on the heart valve; narrowing of a structure (usually a coronary artery) following removal or reduction of a previous narrowing. The majority of patients having angioplasty today are treated with stents. Restenosis can occur after stent implantation and is referred to as "in-stent restenosis." “Stent-in-stent restenosis" is

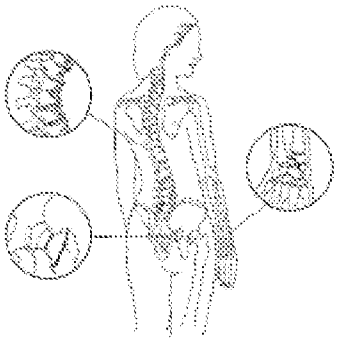
Rheumatoid Arthritis (RA) is a chronic, systemic disease, mainly characterized by inflammation of the synovium of the joints. It can lead to long-term joint damage, resulting in chronic pain, loss of function and disability. RA progresses in three stages. The first stage is the swelling of the synovial lining, causing pain, warmth, stiffness, redness and swelling around the joint. Second is the rapid division and growth of pannus cells causing the synovium to thicken. In the third stage, the inflamed cells release enzymes that may digest bone and cartilage, often causing the involved joint to lose its shape and alignment, more pain, and loss of movement.

Multiple sclerosis (MS) (also known as *disseminated sclerosis* or *encephal-omyelitis disseminata*) is an autoimmune condition in which the immune system attacks the central nervous system, leading to demyelination. Disease onset usually occurs in young adults, and it is more common in women. MS affects the areas of the brain and spinal cord known as the white matter, destroying a fatty layer called the myelin sheath, which wraps around nerve fibers and electrically insulates them. When myelin is lost, the axons of neurons can no longer effectively conduct action potentials. The cause remains unknown. Theories include genetics, infections or different environmental risk factors. Almost any neurological symptom can appear with the disease, and often progresses to physical and cognitive disability. MS has no known cure. Treatments attempt to return function after an attack, prevent new attacks, and prevent disability.

Crohn's Disease (CD) (also called ileitis or enteritis) is an ongoing disorder that causes inflammation of the gastrointestinal (GI) tract. CD can affect any area of the GI tract, from the mouth to the anus, but it most commonly affects the lower part of the small intestine, the ileum. The swelling extends deep into the lining of the affected organ. The swelling can cause pain and can make the intestines empty frequently, resulting in diarrhea. Because the symptoms of CD are similar to other intestinal disorders, such as irritable bowel syndrome and ulcerative colitis, it can be difficult to diagnose. Ulcerative colitis causes inflammation and ulcers in the top layer of the lining of the large intestine. In CD, all layers of the intestine may be involved, and normal healthy bowel can be found between sections of diseased bowel.

Diabetes mellitus is a group of metabolic diseases characterized by high glucose levels that result from defects in insulin secretion, or action, or both. Normally, blood glucose levels are tightly controlled by insulin, a hormone produced by the pancreas. Insulin lowers the blood glucose level. When the blood glucose elevates after eating food, insulin is released from the pancreas to normalize the glucose level. In patients with diabetes, the absence or insufficient production of insulin causes hyperglycemia. Diabetes is a chronic controllable medical condition, but lasts a lifetime.

Ulcerative colitis is a disease that causes inflammation and ulcers in the lining of the rectum and colon. Ulcers form where inflammation has killed cells that usually line the colon, then bleed and produce pus. Inflammation in the colon also causes the colon to empty frequently, causing diarrhea. When the inflammation occurs in the rectum and lower part of the colon it is called ulcerative proctitis. If the entire colon is affected it is called pancolitis. If only the left side of the colon is affected it is called limited or distal colitis. Ulcerative colitis is an inflammatory bowel disease (IBD), the general name for diseases that cause inflammation in the small intestine and colon. It can be difficult to diagnose because its symptoms are similar to other intestinal disorders and to another type of IBD called Crohn's disease. Crohn's disease differs because it causes inflammation deeper within the intestinal wall and can occur in other parts of the digestive system including the small intestine, mouth, esophagus, and stomach.



In **Osteoporosis**, bones become fragile and more likely to break. If not prevented or if left untreated, osteoporosis can progress painlessly until a bone breaks. These

broken bones (fractures) occur typically in the hip, spine and wrist. Any bone can be affected, but of special concern are fractures of the hip and spine. A hip fracture almost always requires hospitalization and major surgery. Spinal or vertebral fractures also have serious consequences, including loss of height, severe back pain, and deformity.

Transplant rejection reactions have traditionally been categorized as "hyperacute, acute or chronic" rejection, based on the clinical tempo of the response and on the pathophysiologic mechanisms involved. In practice, there can be overlap of features and ambiguity in diagnosis. The diagnosis of transplant rejection is further complicated by toxic effects of immunosuppressive drugs and the potential for either mechanical problems (e.g., vascular thrombosis) or recurrence of original disease (e.g., some types of glomerulonephritis). Each transplanted tissue type exhibits its own unique problems.

Cachexia involves weight loss, muscle atrophy, fatigue, weakness and significant appetite loss in one not actively trying to lose weight. It can be a sign of various underlying disorders, e.g., cancer, metabolic acidosis (from decreased protein synthesis and increased protein catabolism), certain infectious diseases (e.g. tuberculosis, AIDS), and some autoimmune disorders, or addiction to drugs such as amphetamines or cocaine. Cachexia physically weakens patients to a state of immobility stemming from appetite loss, asthenia and anemia. Response to standard treatment is usually poor.

The claimed scope includes treating all of these disorders/diseases, which are inadequately enabled based on PDE-4 inhibition. The Formula (I) compounds are disclosed to inhibit PDE-4 and the specification asserts these compounds are there-fore useful to treat all diseases noted above for which Appellants provide insufficient

competent evidence. Further, Appellants have not provided sufficient competent evidence that the instantly disclosed tests (pages 21-28, *inter alia*) are highly predictive for all uses disclosed and embraced by the claim language for the intended host.

(2) The nature of the invention and predictability in the art:

The invention is directed toward medicine and is physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance:

The direction and guidance provided is very limited. The dosage range information (page 83+, *inter alia*) is vague and meager. Even the broadest range is 25 fold. Moreover, this dosage information is generic, the same for the many disorders covered by the specification. There is no specific direction or guidance regarding a therapeutic regimen or dosage effective specifically for various compounds described for various medical conditions comprehended.

In *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 86 USPQ2d 1196, 1202 (Fed. Cir. 2008), Mylan Labs. challenged the enablement of a patent to *Ortho-McNeil Pharm.* J. Rader noted three specific informative instances of the enabling teachings of the *Ortho-McNeil* patent there at issue:

> [1] …the average adult requires 30-2000 milligrams of the claimed compounds administered in two to four doses of 10-500 milligrams. [2] The specification also teaches a skilled artisan to use the claimed compounds in a manner similar to the drug phenytoin. [3] Further the specification directs the reader to a reference by L.S. Goodman, which

> teaches that after establishment of a low initial dose, the dosage is increased at appropriate intervals as required for control of seizures or as limited by toxicity with further adjustments according to plasma drug concentrations. …

(Numbering added.) Such types of information are completely lacking in this specification. Moreover, the dosage is generic; the same for the many disorders covered by the claims. The claims cover more than twenty different types of diseases and the specification fails to provide this information, approvingly noted by J. Rader, for the present methods in regard to these diseases. *Ortho-McNeil* supports this rejection for lack of enablement.

(4) State of the Prior Art:

These compounds are tetrahydropyridazine and dihydropyridazone derivatives with a particular 2-position substitution pattern. So far as this record shows, no structurally similar tetrahydropyridazines and dihydropyridazones have been determined to have PDE-4 inhibition activity, nor to useful for the treatment of the various diseases construed by the claims. Appellants base many of their arguments on the asserted utility of Rolipram, which has no chemical or structural similarity to the compounds of the claimed methods. Wikipedia, Rolipram, downloaded 8/20/2008, http://en.wikipedia.org/wiki/Rolipram.

The comments of Dyke, et al., Exp. Opin. Invest. Drugs 8:1301-1325 (1999) (already of record) on PDE-4 inhibitor efficacy in memory disorders are prophetic (p.1314). Regarding MS, Dyke suggests, with no clinical data available, that PDE4 inhibitors may be useful as anti-inflammatory agents, but not as disease modifying agents (pg. 1313). Dyke's expert opinion was that, although PDE-4 inhibitors may show

promise in the respiratory area, "clinical data in most [other] therapeutic areas with compounds of this class is inconclusive" (pg. 1314). Dyke acknowledges various PDE isoenzymes, but teaches that PDE-4 inhibitors have only been implicated for anti-inflammatory conditions (pg. 1302).

Hanifin, et al., J. Investigative Dermatology, 107(1):51-56 (1996) (already of record) reported testing CP80633, CP102995 and CP76593, PDE-4 inhibitors, on atopic dermatitis. Although Hanifin demonstrated clinical efficacy, later researchers, e.g., Griffiths, et al., British J. Dermatology 2002; 147:299-307 (already of record) noted that CP80633 was "the only PDE-4 inhibitor known to be clinically effective in atopic dermatitis" (p. 300). Thus, Hanifin and Griffiths support that not all PDE-4 inhibitors, such as the claimed compounds, are effective against atopic dermatitis.

PDE-4 predominates in inflammatory cells and, specifically, modulates leucocyte activation. PDE-4 inhibitors would be expected to produce bronchodilation and have a certain anti-inflammatory effect, in particular, blocking mediator synthesis (and release) in mast cells and basophiles.

The concept that PDE-4 inhibitors could treat such pathological conditions/diseases generally is contrary to what is known about PDE-4 inhibitors. Some PDE4 inhibitors cause vasculitis (blood vessel inflammation), which has hindered PDE-4 inhibitor clinical investigation. Development of SCH-351591 halted because of acute and chronic vasculitis in small to medium sized arteries, and vasculitis was a significant problem with CI-1018 and Ariflo® (cilomilast). The PDE-4 inhibitor IC542

triggered a generalized inflammatory response with extensive neutrophil infiltration in the gastrointestinal tract, nearby mesentery and thymus.

(5) Working Examples:

Examples 1-7 show production of a meager number of compounds from among the trillions covered by Formula I. No *in vivo* biological data is presented. *In vitro* testing is shown only for inhibition of proliferation of T-cells (Example I) and control of cytokine production in human PBMCs (Example II). The working examples do not show formation of pharmaceutically acceptable salts or stereoisomers of compounds of Formula I, which are encompassed by the method claims. Regarding such salts and stereoisomers, *Morton Intrntl. Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190, 1194 (Fed.Cir. 1993) stated:

> The specification purports to teach, with over fifty examples, the preparation of the claimed compounds … However … there is no evidence that such compounds exist … [T]he examples … do not produce the postulated compounds …

(6) Skill of those in the art:

The history of the effectiveness of PDE-4 inhibitors is very short. PDE-4 inhibitors have been investigated for disorders including Alzheimer's Disease (AD), chronic obstructive pulmonary disease (COPD), depression, schizophrenia and chronic lymphocytic leukemia. Except for asthma, such efforts have met with little success. The skill level in the area of PDE-4 therapeutics must therefore be considered to be low. At the time of filing and up to now, FDA has not approved any PDE-4 inhibitor for any disorder treatment. Extensive effort to get cilomilast and Daxas® (roflumilast) to be effective against COPD has been without success, evidence of the skill level in this art.

The specification does not describe whether these claimed compounds affect the same isoenzymes as cilomilast and roflumilast.

Many if not most diseases said to be treatable by PDE-4 inhibition, e.g., multiple sclerosis, graft rejection, gastrointestinal disorders, such as ulcerative colitis and Crohn's disease, septic shock, contact dermatitis, dementia, etc., are hard to treat. At present no known drug successfully reverses the course of many of these diseases, including multiple sclerosis (MS), etc., despite many drugs said to inhibit PDE-4.

The state of the art indicates the requirement for undue experimentation. MacKenzie, Allergology International (2004) 53: 101-110 (already of record) indicates that, although the new generation of PDE-4 inhibitors "display[s] greatly reduced side-effects, … further study of the potential ancillary involvement of adrenaline and/or glucocorticoids in the enhancement of PDE-4, shown in blood mononuclear white cells of [atopic dermatitis] patients is warranted." The ability of a PDE-4 inhibitor to treat all diseases/conditions of the present claims remains open to further study and proof.

(7) The quantity of experimentation needed:

Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. See *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). Also, note *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding testing types needed to support *in vivo* use. See also MPEP 2163, *et. seq*. The application disclosure is insufficient to enable instantly claimed methods based solely on disclosure of inhibition of proliferation

of T-cells (Example I) and control of cytokine production in human PBMCs (Example II) by Formula (I) compounds. Such experimentation is potentially open-ended.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

(10) Response to Arguments

Appellants assert that the compounds of Formula I inhibit PDE4 and thus are effective to treat all of the diseases recited by the claims. However, the specification in Examples I and II, at pages 93-94, establishes that compounds of Formula I were only demonstrated to inhibit proliferation of T-cells (Example I) and to control cytokine production in human PBMCs. These are the only methods of use supported by this disclosure and any claims to methods of using the present compounds of Formula I must be limited thereto.

Appellants cite *Ex parte Janin*, 209 USPQ 761 (BOPAI 1979) (Appeal Brief, page 3), for the premise that an unsupported suggestion that reactants within a class defined by the claims are inoperable for a method of use cannot be the basis for claim rejection. However, that is not the basis of the rejection here. Examples I and II establish that Formula I compounds inhibit proliferation of T-cells and control cytokine production in human PBMCs. The specification does not disclose more than that for Formula I

compounds. Also, the present rejection is not a mere "unsupported suggestion," but is amply supported by the documentation cited and discussed herein.

Appellants cite *In re Marzocchi*, 169 USPQ 367 (CCPA 1971) (Appeal Brief, page 3) for the premise that reasons or evidence must be advanced to challenge Appellants' assertion that all compounds encompassed by the claims are operative for the claimed method. Appellants' assertion of utility by claims 21, 24-26 and 30 is supposedly based on the presence of PDE4 inhibitory action in the compounds of Formula I. The references previously of record to Dyke, Hanifin, Griffiths, MacKenzie, Bernes, Kobayashi, Reffelmann, Rybalkin, Lehnart, Xu, Yamaki, Abbas, inter alia for the reasons discussed herein, well establish that the ability of a PDE-4 inhibitor to treat all diseases/conditions of the present claims remains open to further study and proof.

Appellants cite *In re Angstadt*, 190 USPQ 214 (CCPA 1976) and *In re Dinh-Nguyen*, 181 USPQ 46 (CCPA 1974) (Appeal Brief, page 4) in support of their position that it is not necessary for Appellants' method claims to exclude inoperative embodiments, inasmuch as the claims are interpreted in light of the level of understanding of one of ordinary skill in the art. This assertion is true, as far as it goes. However, note that *University of Rochester v. G.D. Searle & Co.*, 68 USPQ2d 1424, 1435 (U.S. District Court, Western District of New York, 2003), citing Angstadt, noted that a key consideration in the question of enablement is whether or not any experimentation is undue. In this situation, the discussion of the prior art literature references herein well establishes that undue experimentation would be necessary even to determine which of the many embodiments covered by the present claims would be operative or inoperative.

In regard to *Dinh-Nguyen*, Appellants are invited to the discussion at 181 USPQ at 47, in which the CCPA required that an assertion by Patent and Trademark Office (PTO) that enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating doubts so expressed. The present record, including the discussion of the prior art literature references herein above (and following below) well establishes evidence and reasoning substantiating the doubts of the enablement of the rejected claims expressed in the rejection of record.

Appellants cite *In re Colianni*, 195 USPQ 150 (CCPA 1977) (Appeal Brief, page 5) for the proposition that determination of undue experimentation must be considered on a compound by compound or indication by indication basis. As above noted, the discussion of the prior art literature references herein above (and following below) well establishes evidence and reasoning substantiating the doubts of the enablement of the rejected claims as expressed in the rejection of record on an indication by indication basis. In *Ex parte Sudilovsky*, 21 USPQ2d 1702 (BPAI 1991), the Board of Patent Appeals and Interferences, citing Judge Miller's concurring opinion in *Colianni*, enumerated factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, paragraph 1. Among these factors are:

1) the nature of the invention,

2) the state of the prior art,

3) the predictability or lack thereof in the art,

4) the amount of direction or guidance present, and

5) the presence or absence of working examples.

Each of these factors and more have been fully considered on this record in reaching the conclusion that the rejected claims do not satisfy the enablement requirement of 35 U.S.C. 112, paragraph 1.

Appellants cite *In re Borkowski*, 164 USPQ 642 (CCPA 1970) (Appeal Brief, page 5) for the proposition that satisfaction of the enablement requirement does not require working examples. Appellants are indeed correct. The *Borkowski* court recognized, 164 USPQ at 645, "a specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation." In *Gould v. Mossinghoff*, 229 USPQ 1, 14 (U.S. District Court District of Columbia, 1985), among the district court's conclusions of law, citing *Borkowski*, was "A patent specification must be enabling as to 'the invention' as set forth in the claims. Thus, a disclosure may be insufficient for one claim but sufficient for another." The patent specification is enabling as to claims 1-19, which have been allowed. The patent specification is not enabling as to claims 21, 24-26 and 30, which are rejected under 35 USC 112, first paragraph. Since the state of the prior art establishes that one skilled in the art would not be able to practice the invention of claims 21, 24-26 and 30 without an undue amount of experimentation, this rejection is proper and sustainable.

Appellants cite *In re Anthony*, 162 USPQ 594 (CCPA 1969) for the proposition that the PTO cannot require the types of proof of effectiveness and safety required by the FDA. Although Appellants are again correct, *Anthony* involved a rejection under 35 USC 101 and is not otherwise germane to the present rejection.

A careful reading of the documents cited by Appellants, supposedly in support of their position, further call into question the ability of all compounds that inhibit PDE4 activity to treat all of the present claimed illnesses.

EP 731099 has been studied but is considered to be rather self-serving on the part of the inventors.

Yamaki, et al., J. Pharm. & Pharm., 2004, 56, 877-882, limits its observations to Rolipram and concludes with an invitation to further research, "…PDE IV inhibitors can be effective in treating Th1-mediated diseases such as RA [rheumatoid arthritis]."

Xu, et al., Invest. Ophthal. & Vis. Sci., April 1999, Vol. 40, #5, 842-950 similarly limits its observations to the single drug, Rolipram, and suggests its use in therapy of the specific disease, Experimental autoimmune uveoretinitis (EAU), a cell-mediated model of retinal autoimmunity that is negatively regulated by interleukin (IL)-10. The present claims do not recite a method of treating the specific disease EAU.

Abbas, et al., Autoimmunity 2000, 32, 2, 93-99 (see complete article attached), limited their research to experimental autoimmune neuritis [EAN], which is also not one of the diseases recited by the present method claims. Abbas noted differences in the action of Rolipram based on dosage: "We found that low dose of Rolipram suppresses clinical signs of EAN more than high dose of Rolipram, but high dose of Rolipram suppress IFN-γ and MIP-1α, MIP-2 and MCP-1 production more than low dose of Rolipram in scatic [*sic* – sciatic?] nerves." Although the present claims to not recite dosage, the dosage range information in the specification (page 83+, *inter alia*) is vague and meager. Even the broadest range is 25 fold. Moreover, this dosage information is

generic, the same for the many disorders covered by the rejected claims. There is no specific direction or guidance regarding a therapeutic regimen or dosage effective specifically for various compounds described for various diseases comprehended. Abbas concluded with a "… call for further studies on the potential role of Rolipram in the treatment of autoimmune diseases."

Regarding allergies and inflammatory diseases, Bernes, J. Allergy Clin. Immunol, Jul. 2000, pgs. 5-16, report, "most of the PDE4 inhibitors so far tested clinically have had unacceptable side effects, particularly nausea and vomiting. … [S]ubtype-selective inhibitors [of PDE4 isoforms] may be developed that may preserve the anti-inflammatory effect, while having less likelihood of side effects." Neither the present claims nor the present specification acknowledges that any of the compounds of Formula I show effectiveness for specific isoforms of PDE4.

Kobayashi, et al., Mediators of Inflammation, Vol. 2007, Article ID 58901, 9 pgs., merely "suggest that PDE4 inhibitors may be therapeutic agents for various diseases such as asthma … and rheumatoid arthritis."

Regarding coronary disease, Reffelmann, et al., Circulation 2003:108;239-244, note, "In the human pulmonary circulation, the [PDE] isoforms 1, 3, 4 and 5 seem to be involved in regulating pulmonary resistance," but suggests a promising future only for PDE5 and not the other isoforms.

Regarding restenosis and atherosclerosis, Rybalkin, et al., Circ. Res. 2002;90;151-157, report disappointing results, "Because PDE3 and PDE4 isozymes are present in the normal arterial wall as well as in many other tissues, inhibition of these

PDEs is likely to cause side-effects, such as vasodilation, nausea, and cardiac arrest." They see a promising future for only one isozyme, PDE1C, "Future studies will reveal if PDE1C can indeed be targeted to inhibit human SMC [smooth muscle cell] proliferation in restenosis after angioplasty, in-stent restenosis, or in lesions of atherosclerosis."

Lehnart, et al., Cell, Vol. 123, 25-35, Oct. 7, 2005, cautions, "These data suggest that reduced PDE4D activity causes defective RyR2-channel [ryanodine receptor] function associated with heart failure and arrhythmias."

The state of the prior art establishes reasons and evidence to doubt the assertion of enablement by the specification. Appellants' statement that claims are to be interpretted in light of the level of understanding of one of ordinary skill in the art is acknowledged as true and supports the basis for the present rejection. The prior art medical articles summarized above establish that one of ordinary skill in this art recognizes that the presence of PDE4 inhibitory activity in a compound does not, in and of itself, establish that that compound will treat all of the illnesses recited in the rejected claims. The use of PDE4 inhibitors to treat various diseases of the claims is not well established and is not well understood by those of skill in the art. This has been established on an indication by indication basis by the discussion of the state of the prior art.

Sitrick v. Dreamworks LLC, 85 USPQ2d 1826, 1830 (Fed. Cir. 2008) decided that a claim is not enabled when the claim covers multiple embodiments but the specification fails to enable all of the embodiments. "Because the asserted claims are broad enough to cover both [embodiments], the [specification] must enable both embodiments." Here, the claims at issue cover many embodiments and do not enable any of them.

Automotive Tech. Int'l. v. BMW of N. America, Inc., 84 USPQ2d 1108, 1116 (Fed. Cir. 2007) decided that a claim is not enabled when the claim covers multiple embodiments but the specification fails to enable one of the embodiments. "Thus, in order to fulfill the enablement requirement, the specification must enable the full scope of the claims that includes both [embodiments], which the specification fails to do." Here, the claims at issue cover many embodiments and do not enable any of them.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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